

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION OF A CEPHALOSPORIN ANTIBIOTIC

Field of the Invention

This invention relates to a sustained release pharmaceutical
5 composition comprising at least a cephalosporin antibiotic, a mixture of
polymers, and other pharmaceutically acceptable excipients. The polymers are
selected from mixture comprising of galactomannans and neutral swellable
polymers, which release the active ingredient in a predetermined manner, said
galactomannans being selected from the group consisting of xanthan gum and
10 neutral swellable polymer selected from the group consisting of poly (ethyl
acrylate: methyl methacrylate) 2:1.

Background of Invention

While many compounds are known to be useful as pharmacologically
active substances, some of them have relatively short biological half life and
15 needs to be administered several times a day in order to achieve desired
therapeutic effects. Especially, the drugs used in treatment of microbial
infections are required to be given more than once during a dosage regimen.

In an anti-microbial therapy the main requirement is to maximize the
blood concentration, preferably several folds higher than the minimum
20 inhibitory concentration (MIC) for the active agent, yet to minimize both the
risk of toxicity to the patient and of promoting microbial resistance. Although
oral administration will be the preferred route, in the case of antibiotics this
route is frequently unattractive because of their low or variable oral
bioavailability. In addition extremely high plasma concentrations of antibiotics
25 are frequently required to achieve the MIC values towards certain gram
negative bacteria (antibiotics and chemotherapy; anti-infective agents and their
use in therapy 7th edition Ed. by O'grady F, Finch RG, Lambert HP;
Greenwood D; Churchill Livingstone 1997).

Sustained release preparation of drugs are advantageous as the administration frequency can be reduced by maintaining a constant plasma concentration of drug over an extended period of time to ensure sustained effect of active ingredient well above the MIC levels. In addition, these
5 preparations are also expected to decrease side effects by suppressing the rapid rise in the blood levels of the drug.

This has been primarily achieved by development of a novel drug delivery system utilizing diverse techniques and principles. Amongst these, known in the art is one such delivery system, which employs hydrophilic
10 polymers to sustained or modified release pharmaceutical composition. For modified release solid dosage forms comprising a drug dispersed uniformly in mixture of polymers, release of the drug is controlled primarily by diffusion of the drug, or by surface erosion of the hydrophilic polymers into the surrounding medium or by a combination of both processes. Control of the
15 rate of release can produce constant blood levels of the active ingredient that may result in reducing the frequency of administration, thereby improving patient compliance to the dosage regimen.

The relevant prior art methods, which teach adaptation of diverse delivery system for sustained release of the active ingredient, are as follows:

20 United States Patent No. 6,120,803 discloses an active agent dosage form, which is adapted for retention in the stomach and useful for the prolonged delivery of an active agent to a fluid environment. The active agent dosage form is a polymer composition that swells upon contact with the fluid of the stomach. A portion of the polymer composition is surrounded by a band
25 of insoluble material that prevents the covered portion of the polymer composition from swelling and provides a segment of the dosage form that is of sufficient rigidity to withstand the contraction of the stomach and delay expulsion of the dosage form from the stomach until substantially all the active agent has been dispensed.

United States Patent No. 5,128,142 discloses a controlled release formulation comprising an absorbate of a mixture of pharmaceutically active ingredients and an inactive substance absorbed on a cross-linked polymer. The inactive substance is selected to modify the dissolution of active ingredients
5 from the cross linked polymer *in vivo*. The inactive substance is preferably present in the absorbate in an amount of 0.5 - 3 parts by weight relative to 1 part by weight of the active ingredients.

United States Patent No. 4,968,508 discloses a sustained release matrix tablet comprising from about 0.1% to about 90% by weight of Cefaclor, about
10 5% of about 29% by weight by hydrophilic polymer and about 0.5% to about 25% by weight of an acrylic polymer which dissolve at a pH in the range of about 5.0 to about 7.4, the total weight of polymers being less than 30% by weight of the formulation. Although a specific Cefaclor formulation is claimed the text suggests that the matrix formulation is suitable for weakly basic drugs
15 and particularly suitable for Cephalexin and Cefaclor.

International Publication number WO 02/41876 discloses a pharmaceutical composition in the form of a tablet for controlled release of an active ingredient comprising a cephalosporin antibiotic such as Cephalexin, Cefaclor or their pharmaceutically acceptable hydrates, salts or esters as active
20 ingredients, and a mixture of hydrophilic polymers selected from the group consisting of at least one sodium alginate and at least one xanthan gum as controlled release matrix and optionally probenecid as an antibiotic adjuvant as either immediate release or controlled release part. The composition may contain one or more of a water soluble and/or water dispersible diluent. The
25 quantity of the hydrophilic polymers matrix still provides the desired once a day profile.

International Publication number WO 02/36126 discloses a fast disintegrating controlled release oral composition comprising a core material containing Cefuroxime axetil present as controlled release form, the

Cefuroxime axetil being provided with an outer coating of a copolymer selected from aqueous dispersions of enteric methacrylic acid and methacrylic acid esters anionic copolymers having carboxyl group as the functional group or mixture thereof and an inner coating of a sustained release copolymer
 5 selected from aqueous dispersions of acrylate or methacrylate pH independent copolymers having quaternary ammonium group as a functional group or mixture thereof. Additionally the coating composition may contain plasticizers. The composition is suitable for once daily administration.

United States Patent No. 4,250,166 discloses a long acting Cephalexin
 10 preparation comprising of normal quick releasing Cephalexin and particulate Cephalexin coated with a copolymer of methacrylates and methacrylic acid which dissolves at pH from 5.5 to 6.5 and the potency ratio of the normal Cephalexin to coated Cephalexin is between 40:60 and 25:75.

United States Patent No. 6,399,086 discloses a controlled release
 15 cephalosporin antibiotic agent preferably Amoxicillin trihydrate in a hydrophilic and / or hydrophobic polymer matrix such that at least 50% but not more than 67.61 ± 5.78 % of the active agent is released within 3 to 4 hrs from oral administration and remainder is released at a controlled rate from the said composition. The composition teaches the use of commonly used
 20 hydrophilic polymers such as hydrophilic cellulose derivatives, hydrophilic methacrylic acid derivatives, chitosan, and alginates. Preferably, they have used hydrophilic cellulose derivative such as methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose. The hydrophobic polymers used in the invention are acrylamides and polyamido derivatives and hydrophobic
 25 methacrylic acid derivatives. The preferred hydrophobic polymer is ethyl cellulose. However with this profile wherein $67.61 \pm 5.78\%$ of the drug is already out of the matrix, and considering a very short half-life of most cephalosporins such as Cephalexin and Cefprozil (55 min and 70 min) respectively the drug profile achieved cannot be suitable for once daily

administration. Hence, it is necessary that the matrix formulation should release the drug over extended period of time.

The corresponding International Publication number WO 98/22091 discloses a controlled release oral drug delivery system comprising as active ingredient a beta-lactam antibiotic having a specific absorption site in a small intestine in a hydrophilic and / or hydrophobic polymer matrix such that at least 50% of the active agent is released within 3 to 4 hrs from oral administration and remainder is released at a controlled rate from the said composition.

10 United States Patent No. 6,083,532 discloses a sustained release tablet comprising a drug to be released at a controlled rate and a sustained release formulation comprising at least three different types of polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer. The pH dependent gelling polymer comprises at least one of
15 an alginate, a carboxyvinyl polymer, or a salt of a carboxymethyl cellulose. The pH independent gelling polymer comprises at least one of a HPMC, HPEC, a HPC, a HEC, a methylcellulose, a xanthan gum or a polyethylene oxide. The enteric polymer comprises at least one of a polyacrylate material, a cellulose acetate phthalate, a cellulose phthalate hydroxy propyl methyl ether,
20 a polyvinyl acetate phthalate, a hydroxy propyl methyl cellulose acetate succinate, a cellulose acetate trimellitate or a shellac.

United States Patent No. 5,948,440 discloses a controlled release tablet of an active ingredient comprising of Cefaclor, Cephalexin or their pharmaceutically acceptable hydrates, salts or esters as active ingredients and
25 a mixture of hydrophilic polymers selected from the group consisting of at least one hydroxy propyl methylcellulose and at least one hydroxyl propyl cellulose. The composition optionally also contains one or more of a water soluble or water dispersible diluent, the quantities are such that the

therapeutically effective active ingredient is released at a rate for twice daily administration of the pharmaceutical composition.

Japanese Patent JP 57165392A discloses a long acting Cephalexin tablet comprising Cephalexin mixed with $\geq 10\%$ w/w oils and fats (e.g. higher fatty acid, higher alcohol, alcohol ester etc) and with a vehicle such as magnesium stearate and the mixture is pressed, formed into granules passing through a 20 mesh sieve, and subjected to the slug formed process to obtain a high quality long acting tablets. The rate of dissolution of Cephalexin can be controlled by selecting the kind of oils and fats and the number of the time of slug formation process.

International Publication number WO 00/15198 teaches controlled delivery pharmaceutical composition having temporal and spatial control, comprising a drug, a gas generating component a swelling agent, a viscolyzing agent and optionally a gel forming polymer. The viscolyzing agent initially and the gel forming polymer thereafter form a hydrated gel matrix which entraps the gas, causing the tablet to float so that it is retained in the stomach thereby providing spatial control and at the same time resulting in sustained release of the drug providing temporal control.

The combination of gas generating component, swelling agent and viscolyzing agent results in the controlled drug delivery systems. Thus all these components are essential for achieving the temporal and spatial control. A preferred once daily Ciprofloxacin formulation comprising 69.9% Ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium bicarbonate, 12.1% cross linked polyvinyl pyrrolidone and optionally other excipients is disclosed.

Sustained release preparation of drugs are advantageous in the administration, frequency can be reduced by maintaining a constant plasma concentration of drug over an extended period of time to ensure sustained effect of active ingredient.

Since the antibiotics are high frequency / high dosing, extended release drug delivery systems have not been very successful in reducing the frequency. The present invention is based on the observation that the release of active ingredient from the delivery system is controlled by the specific
5 polymers present in the matrix and in specific concentrations, thus allowing blood levels above MIC over extended period of time such that the frequency of the dosage form administration can be reduced to twice daily or once daily.

Objective of the Invention

The main objective of the present invention is to provide sustained
10 release pharmaceutical compositions, which have blood levels above MIC over extended period of time.

Another objective of the present invention is to provide sustained release pharmaceutical compositions suitable for twice daily or once daily dosage form.

15 Yet another objective of the present invention is to provide sustained release pharmaceutical compositions, which release the active ingredient in a predetermined manner.

Yet another objective of the present invention is to provide sustained release pharmaceutical compositions of a cephalosporin antibiotic.

Summary of the Invention

Accordingly, the present invention relates to a sustained release pharmaceutical composition comprising a cephalosporin antibiotic, a mixture of galactomannans and neutral swellable polymers and other pharmaceutically acceptable excipients. The polymers are selected in such a way to give
25 sustained release of the active ingredient in a predetermined manner.

Preferably, the invention relates to sustained release pharmaceutical compositions comprising a cephalosporin antibiotic, a mixture of galactomannans and neutral swellable polymers, said galactomannans being selected from the group consisting of xanthan gum and neutral swellable

polymer selected from the group consisting of poly (ethyl acrylate: methyl methacrylate) 2:1.

More preferably, the present invention relates to the sustained release pharmaceutical composition which comprises about 30% to about 90% by weight of a cephalosporin antibiotic; about 1% to about 30% by weight of mixture of polymers comprising from about 0.1% to about 15% by weight of galactomannans, and about 0.1% to about 15% by weight of neutral swellable polymer by weight of sustained release composition.

Still more preferably, the present invention relates to the sustained release pharmaceutical composition comprises about 30 % to about 90 % by weight of cephalosporin antibiotic, about 1 % to about 20 % by weight of mixture of polymers comprising of galactomannans in an amount from about 0.1 % to about 12 % by weight and neutral swellable polymer in an amount from about 0.1 % to about 12 % by weight of sustained release composition.

According to yet another embodiment of the present invention, the sustained release pharmaceutical composition may be prepared by wet granulation method, the said method comprising the steps of:

- (i) mixing the active ingredient, excipients and galactomannans in a mixer,
- (ii) granulating the mixture with neutral swellable polymer,
- (iii) drying the granules by either tray drier or fluid bed drier,
- (iv) milling the dried granules followed by blending the same with addition of dry binder(s) and lubricant(s),
- (v) compressing the lubricated granules into tablets using a tablet press and, if desired, coating the tablets.

According to still another embodiment of the present invention, the sustained release pharmaceutical composition may be prepared by optionally compacting the mixture and sizing it by passing through a sieve after step (i) mentioned above, then followed by the rest of the steps.

A binder such as low viscosity hydroxypropyl methylcellulose (HPMC) can be added optionally during wet granulation.

The tablets may be optionally coated using conventional coating agents. The composition of the present invention may also be formulated as other
5 sustained release oral dosage forms such as capsules, etc.

Detailed Description of the Invention

In an embodiment of the present invention, cephalosporin antibiotic used as active ingredient include Cephalexin, Cefprozil, Cefditoren pivoxil, Cefadroxil, Cefpodoxime proxetil, Cefuroxime axetil, Cefaclor, Cefamandole,
10 Cefoxitin, Cephalothin, Cephapirin, Ceftizoxime, Cefonicid and their pharmaceutically acceptable hydrates, salts or esters.

In another embodiment of the present invention, the cephalosporin antibiotic may be present in an amount from about 30 to about 90% by weight of the sustained release composition. Further, the cephalosporin antibiotic may
15 be present in the amount from 50 mg to 2000 mg.

In an embodiment of the present invention, the galactomannans used is selected from the group consisting of xanthan gum, guar gum, locuat bean gum and the like.

In an embodiment of the present invention, the neutral swellable
20 polymer used is Poly (ethyl acrylate: methyl methacrylate) 2:1.

The composition optionally comprises of one or more excipients such as water soluble or water dispersible diluents, binders, lubricant wherein the quantities of galactomannans and neutral swellable polymers, and water soluble / water dispersible diluents are such that the therapeutically effective
25 active ingredients is released at a rate suitable for once or twice daily administration of the dosage form.

The composition may contain one or more pharmaceutically acceptable diluent(s) in amount from about 1% to about 50 % by weight of the total weight of composition.

These diluents may be water soluble or water dispersible. Examples of water soluble diluents that may be used in the present invention include lactose, mannitol, glucose, sorbitol, maltose, dextrates, dextrans and the like. Water dispersible diluents that may be used such as microcrystalline cellulose, 5 pregelatinized starch, calcium carboxymethylcellulose, croscarmellose sodium, sodium starch glycollate, and the like. In the preferred embodiment, the diluent is lactose in amount from about 5 % to about 20 % by weight of the sustained release composition.

The composition may also contain a tablet binder at a concentration in 10 the range of about 0.2 % to about 12 % by weight of the total weight of composition. The binder may include, polyvinyl pyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, gelatin, pregelatinized starch, sugar, copolyvidonum (Plasdone S-630), and the like.

The composition may also contain a tablet lubricant at a concentration 15 in the range of about 0.2 % to about 5 % by weight of the total weight of composition. The lubricant that may be used include, talc, stearic acid, magnesium stearate, colloidal silicon dioxide, calcium stearate, zinc stearate, hydrogenated vegetable oil and the like.

The composition of the present invention may also contain a glidant 20 such as colloidal silicon dioxide.

Xanthan gum is a high molecular weight, anionic, natural heteropolysaccharide gum produced by aerobic fermentation with the organism *xanthomonas campestris*. It contains D-glucose, D-mannose, D-glucuronate in the molar ratio of 2.8: 2.0: 20 and is partially acetylated with 25 about 4.7% acetyl. Xanthan gum also includes about 3.0% pyruvate, which is attached to a single unit D-glucopyromosyl side chain as a metal. It dissolves in hot or cold water and the viscosity of aqueous solutions of xanthan gum is only slightly affected by changes in the pH of solution between 1 and 11.

Xanthan gum has a branched or helical configuration, thus results in excellent water wicking properties. When xanthan gum comes into contact with an aqueous medium of gastrointestinal tract, it hydrates and swells to form a gel. It has good swelling action on contact with an aqueous medium and overcomes the problem encountered by other gums, which either do not hydrate rapidly enough or hydrate too rapidly. Xanthan gum alone when used as a matrix forming agent in sustained release tablets, releases the drug slightly faster in acidic media, due to more rapid initial surface erosion than at higher pH. After hydration of the gum the drug release is essentially pH independent.

During the course of our studies we found that when xanthan gum alone was used as matrix forming agent, the initial release of the cephalosporin was rapid, but the release retarded at later stage due to hydration of xanthan gum to form a gel.

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin	795.32	75.74
Lactose anhydrous	139.18	13.26
Xanthan gum	105.0	10.0
Magnesium stearate	10.5	1.0

Dissolution in USP Apparatus Type I (900 ml 0.1N HCl, 100 RPM) followed by pH 6.8 phosphate buffer is shown below:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	40.0
2	45.3
3	50.2
4	56.4
5	60.2
6	62.1

Xanthan gum polymers that may be used in the present invention include Xantural TM (Kelco), Rhodigel TM available from (Rhodia, USA) and xanthan gum (Jungbunzlauer, Austria.)

- 5 Poly (ethyl acrylate: methyl methacrylate) 2:1 is a latex available only in aqueous dispersion either 30% or 40 % solids including neutral emulsifier. It has no functional group and is practically neutral. Therefore the films formed are insoluble in water or in aqueous medium over the entire pH range. The polymer swells in aqueous media and gives permeable membrane. The
- 10 permeability is independent of pH.

We also found that when poly (ethyl acrylate : methyl methacrylate) 2:1 was used alone the release was retarded, however the tablet integrity was lost after 2 hours.

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin	795.32	75.74
Lactose anhydrous	139.18	13.26
Eudragit NE 30 D	105.0	10.0
Magnesium stearate	10.5	1.0

- 15 Dissolution in USP Apparatus Type I (900 ml 0.1N HCl, 100 RPM) followed by pH 6.8 phosphate buffer is shown below:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	18.9
2	61.76
3	98.6 (Integrity lost)

Poly (ethyl acrylate: methyl methacrylate) 2:1 is available under the brand name of Eudragit NE 30D from Rohm Pharma Company, Germany.

According to the present invention, when a pH independent neutral swellable polymer was mixed with xanthan gum along with active ingredient,
5 the release from the composition was controlled initially and released uniformly over a period of time such that desired blood levels were achieved suitable for twice or once daily dosage form.

The combination of xanthan gum and poly (ethyl acrylate: methyl methacrylate) 2:1 is a unique combination suitable for sustained release of
10 active ingredients, which are to be administered once daily. Both the polymers give a pH independent release profile.

The granulation of the blend of active ingredient, diluent, binder, lubricant and xanthan gum with poly (ethyl acrylate: methyl methacrylate) 2:1 aqueous dispersions, form thinner but more effective film layers, where drug
15 particles and granulating excipients are partially impregnated and during compression they are embedded in a fine network of thin polymer layers. When the tablet comes in contact with aqueous media of the gastrointestinal tract, the thin film of poly (ethyl acrylate: methyl methacrylate) 2:1 controls the penetration of digestive fluids in to the composition and thus avoids initial
20 erosion of xanthan gum, which is high at acidic pH. The poly (ethyl acrylate: methyl methacrylate) 2:1 slowly hydrates without disrupting the hydrophilic composition formed by the heteropolysaccharide. The insoluble poly (ethyl acrylate: methyl methacrylate) 2:1 forms a sponge like structure, which behaves as an inert matrix. Once the xanthan gum is completely hydrated, it
25 forms a gel and then the release of active ingredient is governed by diffusion of dissolved drug through the pores, channels and capillaries of the insoluble polymer composition.

In the present invention it was observed that when these two polymers were mixed together in appropriate concentration to form a tablet, the release

was controlled in such a manner that the dosage form is suitable for once daily administration.

We have found surprisingly that when we control the release of the active ingredients so as to achieve a 14 - 16 hours release profile, we were able
5 to achieve the blood levels suitable for dosage forms for once or twice daily administration.

The present invention is illustrated by the following examples, but is not intended to be limited to the scope of the invention.

Examples

10 General procedure for the preparation of sustained release tablet:

Cephalosporin antibiotic, galactomannans, lactose were screened through 30 mesh sieve and granulated with aqueous dispersions of Eudragit NE 30D by using high shear Mixer granulator or Fluidized bed processor. Granules were dried in either Tray drier or Fluidized bed drier. The dried
15 granules were milled, followed by blending with addition of dry binder such as low viscosity hydroxypropyl methylcellulose and lubricant such as magnesium stearate. The lubricated granules were then compressed to form tablets. These core tablets were optionally coated using conventional coating agents such as hydroxypropyl methylcellulose (HPMC), Opadry™, and
20 plasticizers such as polyethylene glycol, propylene glycol, etc.

The composition of the present invention may also be formulated as other sustained release oral dosage forms such as powders, pellets, minitables, filled into capsules, etc.

Dissolution method:

25 For all the examples containing Cephalixin, Cefprozil or Cefadroxil, wherever specific dissolution conditions are not mentioned, the tablets were tested for Cephalixin, Cefprozil or Cefadroxil in "USP Apparatus Type I (Basket method)" in 900 ml of 0.1N HCl for 1 hour, after which the dissolution media was changed to 900 ml of pH 6.8 phosphate buffer. The

tablets were placed in 40-mesh basket and rotated at 100 RPM, and tested at different specified time points.

- For all the examples containing Cefpodoxime proxetil or Cefuroxime axetil, wherever specific dissolution conditions are not mentioned, the tablets
- 5 were tested for Cefpodoxime proxetil or Cefuroxime axetil in “USP Apparatus Type II (Paddle method)”, paddle rotated at 75 RPM, in 900 ml of Glycine buffer pH 3.0 (0.008M) for 1 hour followed by 900 ml of phosphate buffer pH 6.8, and tested at different specified time points.

Example 1:

10 **Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	798.15	75.74
Lactose anhydrous	188.15	18.26
Xanthan gum	21.0	2.0
Eudragit NE 30D	31.5	3.0
Purified water	q.s.	-
Magnesium stearate	10.5	1.0

Dissolution profile:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	19.25
2	26.44
4	44.0
6	59.57
8	70.4
10	78.5
12	81.9

Example 2:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.32	75.25
Lactose anhydrous	107.68	10.26
Xanthan gum	31.5	3.0
Eudragit NE 30D	52.5	5.0
Purified water	q.s.	-
HPMC E5	52.5	5.0
Magnesium stearate	10.5	1.0

Dissolution profile:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	25.21
2	30.18
4	38.17
6	50.84
8	63.70
10	73.18
12	78.60
14	84.17

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Example 3:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.32	75.24

Lactose anhydrous	97.18	9.26
Xanthan gum	42.0	4.0
Eudragit NE30D	52.5	5.0
Purified water	q.s.	-
HPMC E5	52.5	5.0
Magnesium stearate	10.5	1.0

Dissolution profile:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	22.42
2	30.25
4	41.62
6	48.33
8	54.54
10	60.70
12	66.30
14	71.80

Example 4:**5 Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.32	75.24
Lactose anhydrous	86.68	8.26
Xanthan gum	52.5	5.0
Eudragit NE 30D	52.5	5.0
Purified water	q.s.	-
HPMC E5	52.5	5.0

Magnesium stearate	10.5	1.0
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Dissolution profile :

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	35.57
2	41.96
4	54.46
6	65.00

Example 5:**5 Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.32	75.24
Lactose anhydrous	107.68	10.26
Xanthan gum	52.5	5.0
Eudragit NE 30D	42.0	4.0
Purified water	q.s.	-
HPMC E5	42.0	4.0
Magnesium stearate	10.5	1.0

Dissolution profile:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	26.3
2	31.5
4	39.8
6	47.7
8	51.2

10	56.1
12	62.9
14	69.87

Example 6:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.32	75.74
Lactose anhydrous	107.68	9.26
Xanthan gum	42.0	4.0
Eudragit NE 30D	42.0	4.0
Purified water	q.s.	-
HPMC E5	52.5	5.0
Magnesium stearate	10.5	1.0

5 Dissolution profile:

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	26.4
2	31.4
4	38.7
6	49.5
8	61.7
10	67.8
12	80.0
14	85.2

Example 7:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	806.02	76.76
Lactose anhydrous	33.98	3.24
Xanthan gum	73.5	7.0
Eudragit NE 30 D	73.5	7.0
Purified water	q.s.	-
HPMC E5	52.5	5.0
Magnesium Stearate	10.5	1.0

5 **Dissolution Profile:** USP I, 100 RPM, First two hrs in 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hrs) media (900 ml) change up to 24 hrs.

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	25.3
2	32.9
4	39.2
6	41.6
8	44.2
10	46.9
12	49.9
14	53.7
16	56.6
18	59.7
20	63.2

22	66.6
24	69.9

Example 8:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	806.02	76.76
Lactose anhydrous	86.48	8.24
Xanthan gum	73.5	7.0
Eudragit NE 30 D	42.0	4.0
Purified water	q.s.	-
HPMC E5	31.5	3.0
Magnesium Stearate	10.5	1.0

- 5 **Dissolution Profile:** USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time points (1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 hrs) media (900 ml) change up to 20 hrs.

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	20.4
2	30.2
4	37.0
6	39.0
8	41.7
10	45.6
12	48.6
14	53.3

16	56.7
18	60.4
20	64.0

Example 9:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	806.02	76.76
Lactose anhydrous	54.94	5.24
Xanthan gum	31.5	3.0
Eudragit NE 30 D	42.0	4.0
Purified water	q.s.	-
HPMC E5	105.0	10.0
Magnesium Stearate	10.5	1.0

- 5 **Dissolution Profile:** USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14, 16 and 18 hrs) media (900 ml) change up to 18 hrs.

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	25.9
2	38.2
4	43.1
6	45.9
8	49.4
10	53.1
12	59.5

14	70.2
16	78.7
18	88.0

Example 10:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cephalexin monohydrate (Equiv. to 750 mg Cephalexin)	795.15	75.73
Lactose anhydrous	65.85	6.27
Xanthan gum	73.5	7.0
Eudragit NE 30 D	73.5	7.0
Purified water	q.s.	-
HPMC E5	31.5	3.0
Magnesium Stearate	10.5	1.0

5

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14, 16 and 18 hrs) media (900 ml) change up to 18 hrs.

<i>Time (hour)</i>	<i>Percent Cephalexin Released</i>
1	24.3
2	35.7
4	43.1
6	46.2
8	50.9
10	56.8

12	64.2
14	72.1
16	82.2
18	95.7

Bioavailability studies:

The bioavailability study was conducted for comparison between conventional Cephalexin capsule (500 mg) and each of the sustained release composition formulations of Cephalexin 2 tablets of 750mg, prepared according to the above examples of the present invention. In each of the two studies, eight healthy male volunteers were selected for the study in which each volunteer was administered a dose of the drug with 240 ml of water. The volunteers fasted overnight and had a standard breakfast before taking the drug. The desired blood levels upto 18 to 21 hours were achieved with the compositions prepared according to examples of the present invention, clearly indicating that it can be used for once daily dosing. The comparative pharmacokinetic parameters of the two studies for compositions of examples 9 & 10 are summarized in tables below (Figures 1 & 2)

The cephalosporin antibiotic exhibits minimal concentration dependent killing and produce short term or no persistent effect with most bacteria. The killing rate of these antibiotics saturates at concentrations of around 4 to 5 times the MBC, thus high concentration will not kill the bacteria faster than lower concentrations. It has also been suggested that a concentration much greater than the MIC decreases in bacterial kill potency. These findings have led to the hypothesis that continuously maintained concentrations above a certain level, related to the MIC would be more efficacious than the high peak through concentrations obtained with an intermittent dosing regimen.

From the Pharmacokinetic data obtained, it is seen the sustained release formulation has achieved the Time / MIC approximately equivalent to 3 times the dosing of conventional dosage regime which is essential for killing the bacteria.

5

Comparative pharmacokinetic parameters for composition of example 9:

Parameters	Cephalexin Capsules 500mg	Cephalexin OD (750 mg X 2 T)
C_{max} (mcg/ml)	13.45	20.01
T_{max} (hrs)	2.18	4.87
AUC_{0-t} (mcg.hr/ml)	34.62	100.34

Comparative pharmacokinetic parameters for composition of example 10:

Parameters	Cephalexin Capsules 500mg	Cephalexin OD (750 mg X 2 T)
C_{max} (mcg/ml)	20.10	26.91
T_{max} (hrs)	2.375	4.875
AUC_{0-t} (mcg.hr/ml)	61.29	164.27

10 Example 11:

Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1084.52	77.54
Lactose anhydrous	118.48	8.46
Xanthan gum	56.0	4.0
Eudragit NE 30D	56.0	4.0
Purified water	q.s.	-

HPMC E5	70.0	5.0
Magnesium stearate	14.0	1.0

Dissolution profile :

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	17.4
2	21.2
4	22.0
6	24.2
8	33.1
10	40.2
12	45.6
14	53.0

Example 12:**5 Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1084.52	77.54
Lactose anhydrous	90.48	8.46
Xanthan gum	42.0	3.0
Eudragit NE 30D	28.0	2.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium stearate	14.0	1.0

Dissolution profile :

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	20.3
2	24.4
4	32.1
6	40.8
8	57.4
10	70.5
12	78.5
14	84.8

Example 13:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1066.7	76.19
Lactose anhydrous	81.3	5.81
Xanthan gum	28.0	2.0
Eudragit NE 30 D	70.0	5.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

5

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14 and 16 hrs) media (900 ml) change up to 16 hrs.

10

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	20.8
2	28.4
4	31.4
6	32.9
8	35.8
10	41.4
12	47.6
14	53.2
16	59.1

Example 14:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1066.7	76.19
Lactose anhydrous	95.26	6.81
Xanthan gum	28.0	2.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

- 5 Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time points (1, 2, 4, 6, 8, 10 and 12 hrs) media (900 ml) change up to 12 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	22.4

2	30.3
4	35.2
6	37.0
8	40.4
10	45.0
12	51.0

Example 15:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1048.3	74.9
Lactose anhydrous	99.67	7.1
Xanthan gum	42.0	3.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

- 5 **Dissolution Profile:** USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hrs) media (900 ml) change up to 24 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	29.3
2	39.2
4	43.1
6	46.0

8	48.8
10	51.0
12	54.6
14	58.8
16	65.4
18	72.1
20	77.8
22	84.7
24	95.1

Example 16:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1048.33	74.9
Lactose anhydrous	127.67	9.1
Xanthan gum	84.0	6.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	70.0	5.0
Magnesium Stearate	14.0	1.0

- 5 **Dissolution Profile:** USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hrs) media (900 ml) change up to 24 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	17.1

2	23.4
4	26.3
6	29.0
8	30.5
10	35.0
12	36.9
14	39.1
16	40.3
18	41.3
20	44.6
22	46.7
24	52.5

Example 17:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1048.33	74.9
Lactose anhydrous	57.67	4.1
Xanthan gum	84.0	6.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

- 5 Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time points (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hrs) media (900 ml) change up to 24 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	15.9
2	23.4
4	27.0
6	29.8
8	31.8
10	38.3
12	44.5
14	46.3
16	47.8
18	49.0
20	52.5
22	55.7
24	60.7

Example 18:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1056.52	75.5
Lactose anhydrous	105.48	7.5
Xanthan gum	28.0	2.0
Eudragit NE 30 D	28.0	2.0
Purified water	q.s.	-
HPMC E5	168.0	12.0
Magnesium Stearate	14.0	1.0

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12 and 14 hrs) media (900 ml) change up to 14 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	20.9
2	30.2
4	33.6
6	39.5
8	50.3
10	63.7
12	82.0
14	93.1

5

Example 19:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefprozil monohydrate (Equiv. to 1000 mg Cefprozil)	1070.0	76.43
Lactose anhydrous	35.94	2.57
Xanthan gum	84.0	6.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by

10

Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12 and 14 hrs) media (900 ml) change up to 14 hrs.

<i>Time (hour)</i>	<i>Percent Cefprozil Released</i>
1	18.9
2	22.8
4	33.3
6	43.3
8	54.7
10	65.0
12	77.2
14	88.0

The bioavailability study was conducted for comparison between conventional Cefprozil (500mg) and sustained release composition of Cefprozil (1000mg) of the above example.

- 5 Six healthy male volunteers were selected for the study in which each volunteer was administered a dose of the drug with 180 ml of water. The volunteers fasted overnight and had a US FDA recommended breakfast before taking the drug. The desired blood levels up to 15-16 hrs were achieved with the composition prepared according the present invention, clearly indicating
- 10 that it can be used as once daily dosing. The data is summarized in table below (Figure 3).

Comparative pharmacokinetic parameters:

Parameters	Cefprozil 500 mg (Conventional)	Cefprozil OD 1000 mg
C_{\max} (mcg/ml)	11.18	11.86
T_{\max} (hrs)	2.66	5.75
AUC_{0-t} (mcg.hr/ml)	34.53	67.96

Example 20:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefpodoxime proxetil (Equiv. to 400 mg cefpodoxime)	563.42	56.34
Lactose anhydrous	371.58	37.16
Croscarmellose Sodium	15.0	1.5
Calcium CMC	20.0	2.0
Xanthan gum	10.0	1.0
Eudragit NE 30 D	10.0	1.0
Purified water	q.s.	-
Magnesium Stearate	5.0	0.5
Croscarmellose Sodium	25.0	2.5
Magnesium Stearate	10.0	1.0

Dissolution Profile: USP II, 75 RPM, First hr in Glycine buffer pH 3.0

5

(0.008M) followed by Phosphate Buffer pH 6.8 with
every time point (1, 2, 3, 4 and 5 hrs.) media (900 ml)
change up to 5 hrs.

<i>Time (hour)</i>	<i>Percent Cefpodoxime proxetil Released</i>
1	43.9
2	67.6
3	84.2
4	93.5
5	101.8

The bioavailability study was conducted for comparison between conventional Cefpodoxime proxetil (200mg) bid and sustained release composition of Cefpodoxime proxetil OD (400mg) of the above example.

Twelve healthy male volunteers were selected for the study in which each volunteer was administered a dose of the drug with 240 ml of water. The volunteers fasted overnight and had a US FDA recommended breakfast before taking the drug. The desired blood levels up to 15-16 hrs were achieved with the composition prepared according the present invention, clearly indicating that it can be used as once daily dosing. The data is summarized in table below (Figure 4).

Comparative pharmacokinetic parameters:

Parameters	Cefpodoxime 200 mg bid (Conventional)	Cefpodoxime OD 400 mg
C _{max} (mcg/ml)	3.030	4.223
T _{max} (hrs)	3.542	4.875
AUC _{0-t} (mcg.hr/ml)	34.839	29.148

Example 21:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefuroxime axetil (Equiv. to 500 mg cefuroxime)	614.85	51.23
Lactose anhydrous	153.15	12.76
Croscarmellose Sodium	120.0	10.0
Calcium CMC	36.0	3.0
Copolyvidonum (Plasdone S-630)	60.0	5.0
Xanthan gum	12.0	1.0
Eudragit NE 30 D	12.0	1.0
Purified water	q.s.	-
Hydrogenated vegetable oil	6.0	0.5
Calcium CMC	60.0	5.0
Croscarmellose Sodium	120.0	10.0
Hydrogenated vegetable oil	6.0	0.5

- 10 **Dissolution Profile:** USP II, 75 RPM, First hr in Glycine buffer pH 3.0 (0.008M) followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 3, 4 and 5 hrs.) media (900 ml) change up to 5 hrs.

<i>Time (hour)</i>	<i>Percent Cefuroxime axetil Released</i>
1	31.3
2	56.7
3	78.9
4	91.7
5	96.5

Example 22:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefuroxime axetil (Equiv. to 500 mg cefuroxime)	614.85	51.24
Lactose anhydrous	213.15	17.76
Croscarmellose Sodium	120.0	10.0
Calcium CMC	36.0	3.0
Copolyvidonum (Plasdone S-630)	60.0	5.0
Xanthan gum	12.0	1.0
Eudragit NE 30 D	12.0	1.0
Purified water	q.s	-
Hydrogenated vegetable oil	6.0	0.5
Croscarmellose Sodium	120.0	10.0
Hydrogenated vegetable oil	6.0	0.5

Dissolution Profile: USP II, 75 RPM, First hr in Glycine buffer pH 3.0

- 5 (0.008M) followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 3, 4 and 5 hrs.) media (900 ml) change up to 5 hrs.

<i>Time (hour)</i>	<i>Percent Cefuroxime axetil Released</i>
1	39.3
2	53.1
3	67.4
4	78.4
5	87.4

Example 23:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefuroxime axetil (Equiv. to 500 mg cefuroxime)	614.85	51.24
Lactose anhydrous	153.15	12.76
Croscarmellose Sodium	120.0	10.0
Calcium CMC	36.0	3.0
Copolyvidonum (Plasdone S-630)	60.0	5.0
Xanthan gum	12.0	1.0
Eudragit NE 30 D	12.0	1.0
Purified water	q.s	-
Hydrogenated vegetable oil	6.0	0.5
Calcium CMC	60.0	5.0
Croscarmellose Sodium	120.0	10.0
Hydrogenated vegetable oil	6.0	0.5

Dissolution Profile: USP II, 75 RPM, First hr in Glycine buffer pH 3.0

- 5 (0.008M) followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 3, 4 and 5 hrs.) media (900 ml) change up to 5 hrs.

<i>Time (hour)</i>	<i>Percent Cefuroxime axetil Released</i>
1	31.3
2	56.7
3	78.9
4	91.7
5	96.5

Example 24:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefadroxil monohydrate (Equiv. to 1000 mg Cefadroxil)	1061.96	75.9
Lactose anhydrous	86.04	6.1
Xanthan gum	28.0	2.0
Eudragit NE 30 D	70.0	5.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by

5

Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6,

8,10 and 12 hrs) media (900 ml) change up to 12 hrs.

<i>Time (hour)</i>	<i>Percent Cefadroxil Released</i>
1	26.2
2	36.6
4	41.6
6	44.0
8	46.6
10	50.3
12	55.5

Example 25:Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefadroxil monohydrate	1061.96	75.9

(Equiv. to 1000 mg Cefadroxil)		
Lactose anhydrous	100.04	7.1
Xanthan gum	28.0	2.0
Eudragit NE 30 D	56.0	4.0
Purified water	q.s.	-
HPMC E5	140.0	10.0
Magnesium Stearate	14.0	1.0

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10 and 12 hrs) media (900 ml) change up to 12 hrs.

<i>Time (hour)</i>	<i>Percent Cefadroxil Released</i>
1	25.5
2	37.4
4	42.1
6	44.2
8	46.7
10	49.4

5

Example 26:

Composition:

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefadroxil monohydrate (Equiv. to 1000 mg Cefadroxil)	1061.96	75.9
Lactose anhydrous	100.04	7.1
Xanthan gum	28.0	2.0
Eudragit NE 30 D	28.0	2.0
Purified water	q.s.	-

HPMC E5	168.0	12.0
Magnesium Stearate	14.0	1.0

Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 4, 6, 8, 10, 12, 14 and 16 hrs) media (900 ml) change up to 16 hrs.

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<i>Time (hour)</i>	<i>Percent Cefadroxil Released</i>
1	26.6
2	38.5
4	44.4
6	46.5
8	54.1
10	64.6
12	74.7
14	84.1
16	93.6

Example 27:**Composition:**

<i>Ingredients</i>	<i>Weight (mg / tablet)</i>	<i>% w/w</i>
Cefadroxil monohydrate (Equiv. to 1000 mg Cefadroxil)	1065.21	76.09
Lactose anhydrous	124.79	8.91
Xanthan gum	28.0	2.0
Eudragit NE 30 D	28.0	2.0
Purified water	q.s.	-
HPMC E5	140.0	10.0

Magnesium Stearate	14.0	1.0
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Dissolution Profile: USP I, 100 RPM, First two hrs 0.1 N HCl followed by Phosphate Buffer pH 6.8 with every time point (1, 2, 3, 4, 5, 6, 7 and 8 hrs) media (900 ml) change up to 8 hrs.

<i>Time (hour)</i>	<i>Percent Cefadroxil Released</i>
1	26.2
2	40.0
3	47.1
4	53.6
5	63.4
6	74.5
7	81.5
8	90.4

5

The bioavailability study was conducted for comparison between conventional Cefadroxil (1000mg) and sustained release composition of Cefadroxil OD 1000 mg of the above example.

Eight healthy male volunteers were selected for the study in which each volunteer was administered a dose of the drug with 240 ml of water. The volunteers fasted overnight and had a US FDA recommended breakfast before taking the drug. The desired blood levels up to 8-10 hrs were achieved with the composition prepared according the present invention, clearly indicating that it can be used as once daily dosing. The data is summarized in table below (Figure 5).

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Comparative pharmacokinetic parameters:

Parameters	Cefadroxil 1000 mg (Conventional)	Cefadroxil OD 1000 mg
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C_{\max} (mcg/ml)	24.69	19.30
T_{\max} (hrs)	3.31	4.76
AUC_{0-t} (mcg.hr/ml)	106.0	107.14

While there have been shown and described what are believed to be the preferred embodiments of the present invention, it will be apparent to those of ordinary skill in the pharmaceutical formulating art that various modifications
5 in the formulations and processes herein described can be made without departing from the scope of invention as it is defined by the appended claims

List of Figures :

- Figures 1 & 2 : Plot of comparative plasma profile of Cephalexin OD v/s
10 Cephalexin capsules, for examples 9 & 10 respectively.
- Figure 3 : Plot of comparative plasma profile of Cefprozil OD 1000 mg v/s Cefprozil 500 mg conventional tablets.
- Figure 4 : Plot of comparative plasma profile of Cefpodoxime OD 400 mg v/s Cefpodoxime 200 mg bid conventional tablets.
- 15 Figure 5 : Plot of comparative plasma profile of Cefadroxil OD 1000 mg v/s Cefadroxil 1000 mg conventional tablets.